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C2C
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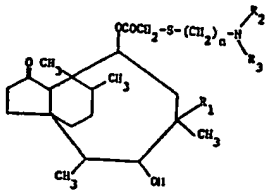
(54) Process for the Production of Pleuromutilin Derivatives

(57) The present invention provides a process for the production of compounds of formula I,



I

in which

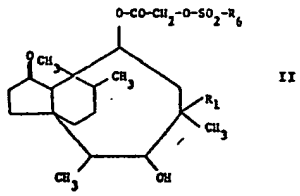
n is 2, 3, 4 or 5

R_1 is ethyl or vinyl, and either

R_2 and R_3 are the same or different and each signifies alkyl of 1 to 4 carbon atoms, or

R_2 and R_3, together with the nitrogen atom to which they are attached, form a heterocyclic ring optionally containing a second hetero moiety selected from oxygen, sulphur or =N—R_5, in which R_5 is alkyl of 1 to 4 carbon atoms,

or an acid addition salt form thereof, comprising reacting a compound of formula II,



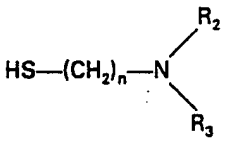
II

in which

R_1 is as defined above, and

R_6 is alkyl of 1 to 4 carbon atoms or phenyl, unsubstituted or substituted by alkyl of 1 to 4 carbon atoms,

with a compound of formula III,



III

in which n, R_2 and R_3 are as defined above, characterised in that the reaction is effected in the presence of a phase transfer catalyst, and, where required, converting a resulting free base form of the compounds of formula I into an acid addition salt form, or *vice versa*.

The compounds of formula I are indicated for use as antibiotics having an antibacterial effect and are also indicated for use as prophylactic additives for animal feeding stuffs and animal drinking water.

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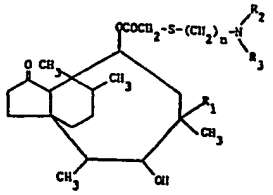
SPECIFICATION

Improvements In or Relating to Organic Compounds

This invention concerns pleuromutilin derivatives.

More particularly, this invention provides a process for the production of compounds of formula I,



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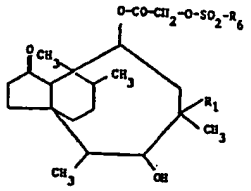
and either

R_2 and R_3 are the same or different and each signifies alkyl of 1 to 4 carbon atoms,

or

R_2 and R_3, together with the nitrogen atom to which they attached, form a heterocyclic ring optionally containing a second hetero moiety selected from oxygen, sulphur or $=N-R_5$, in which R_5 is alkyl of 1 to 4 carbon atoms,

or an acid addition salt form thereof, comprising reacting a compound of formula II,



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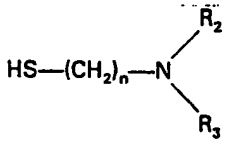


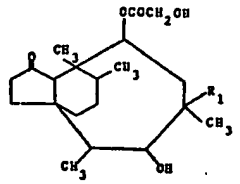
III

in which n, R_2 and R_3 are as defined above, characterised in that the reaction is effected in the presence of a phase transfer catalyst.

The process is suitably effected by addition of a solution of the compound of formula II in an inert, water-immiscible solvent, for example an aromatic solvent, such as toluene, to an aqueous solution of the compound of formula III, which is suitably in the form of an acid addition salt, for example in hydrochloride salt form. The reaction is conveniently effected at a temperature of from 25° to 70°C. Suitable phase transfer catalysts are conventional such catalysts, including benzyl tributylammonium bromide and tetrabutylammonium bromide. The catalyst is conveniently present in catalytic amounts, for example 1 to 2 mol %. The reaction mixture is then suitably made alkaline, for example by addition of aqueous alkali metal hydroxide, e.g. sodium hydroxide solution.

The resulting compounds of formula I may be isolated and purified in conventional manner. Where required, free base forms thereof may be converted into acid addition salt forms in conventional manner, and *vice versa.* Suitable salt forms include the hydrochloride and hydrogen fumarate.

The compounds of formula II are known and may be produced by reacting a compound of formula IV,



IV

in which

R_1 is as defined above,

with a compound of formula V,

$$R_6SO_2A \qquad V$$

in which

A is the acid radical of a reactive ester.

The reaction may be effected in known manner, for example as described in Example 1 hereinafter. "A" suitably signifies chlorine or bromine. The resulting compounds of formula II may, if desired, be isolated and purified using conventional techniques but are preferably employed without isolation in the subsequent step of producing compounds I.

The compounds of formula I are known antibiotics with anti-bacterial activity and may, for example, be used for treating (prophylaxis or therapy) micro-organism infections in domestic animals, e.g. pigs and poultry.

The preferred compounds of formula I are those in which n is 2 or 3, in particular 2. R_1 may be ethyl but is preferably vinyl. R_2 and R_3 are preferably each alkyl of 1 to 4, in particular 1 to 3, carbon atoms, more particularly 2 carbon atoms. They may, however, as indicated, also form a heterocyclic ring together with the nitrogen atom to which they are attached. Such ring suitably contains a second moiety. When the ring contains 6 ring members, this is preferably para to the nitrogen atom. The second hetero moiety is preferably oxygen or, more preferably, $=N-R_5$. R_5 is preferably alkyl of 1 to 2 carbon atoms.

The process of the invention is generally known. It has, however, been found that by carrying out the process in the presence of a phase transfer catalyst, not only are the yields improved somewhat but also the need to isolate the starting material of formula II can be

eliminated. In addition, the process may be effected in solvents such as toluene, which may more easily and completely be regenerated thus leading to decreased environmental problems. Finally, the required reaction time is diminished and working up is simplified.

The following Examples illustrate the invention.

Example 1

14-Desoxy-14-[(2-diethylaminoethyl)-mercapto-acetoxy]mutilin

250 g of 14-desoxy-14-hydroxyacetoxymutilin are suspended in a mixture of 900 ml of toluene and 300 ml of 15% aqueous sodium hydroxide solution, at room temperature. The mixture is heated to about 60°C and mixed, with stirring, with a solution of 138 g of *p*-toluenesulphonyl chloride in 350 ml of toluene. The mixture is stirred for 1½ hours at 60°C and the still warm aqueous phase is separated off. The toluene phase containing 14-desoxy-14-tosyloxyacetoxymutilin is mixed with 112 g of diethylaminoethanethiol hydrochloride, 175 ml of water and 3.5 g of benzyltributylammonium bromide and 165 ml of concentrated caustic soda are added, with stirring to the resulting mixture at 60°C. The mixture is stirred for 2 hours at 60°C, the aqueous phase is then separated off and the toluene phase is extracted with dilute sulphuric acid. The H_2SO_4 extract is made alkaline (pH=12) with 2 N caustic soda and precipitated heading compound extracted with toluene. The toluene solution is evaporated to obtain the heading compound in the form of a yellow oil.

The resulting free base may be treated with fumaric acid in known manner to obtain the hydrogen fumarate salt form, m.p. 148—149°C.

Example 2

In manner analogous to Example 1 and employing appropriate starting materials in approximately equivalent amounts, the following compounds may be obtained:—

14-desoxy-14-[(2-morpholinoethyl)mercapto-acetoxy]mutilin hydrochloride, softening point 70°C,

14-desoxy-14-[(2-diisopropylaminoethyl)-mercaptoacetoxy]-mutilin hydrochloride,

14-desoxy-14-[(di-*n*-butylaminoethyl)-mercaptoacetoxy)-mutilin hydrochloride, softening point 85—90°C

14-desoxy-14-[2-(4-methyl)piperazinoethyl)-mercaptoacetoxy]mutilin dihydrochloride, m.p. 185—188°C,

14-desoxy-14-[(2-dimethylaminoethyl)-mercaptoacetoxy]-dihydromutilin, trimethyl ammonium iodide, softening point 123—128°C,

14-desoxy-14-[3-(di-n-butylaminopropyl)-mercaptoacetoxy]-mutilin hydrochloride, softening point 45—48°C,

14-desoxy-14-[3-(di-n-butylaminopropyl)-mercaptoacetoxy]-dihydromutilin hydrochloride, softening point ~90°C,

14-desoxy-14-[(2-thiomorpholinoethyl)-mercaptoacetoxy]-mutilin hydrochloride, softening point 120—125°C, and

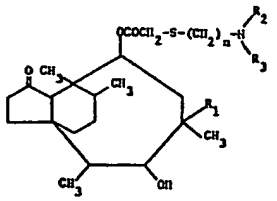
14-desoxy-14-[2-(4-methylpiperazino)ethyl-mercaptoacetoxy]-dihydromutilin, dihydrochloride m.p. 220°—225°C.

Example 3

The procedure of Examples 1 and 2 may be effected in analogous manner but employing tetrabutylammonium bromide in place of benzoyltributylammonium bromide, in an approximately equivalent amount, to obtain the compounds indicated.

Claims

1. A process for the production of compounds of formula I,



I

in which

n is 2, 3, 4 or 5,

R_1 is ethyl or vinyl,

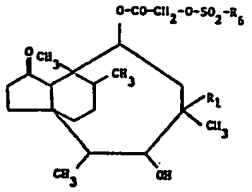
and either

R_2 and R_3 are the same or different and each signifies alkyl of 1 to 4 carbon atoms,

or

R_2 and R_3, together with the nitrogen atom to which they are attached, form a heterocyclic ring optionally containing a second hetero moiety selected from oxygen, sulphur or =N—R_5, in which R_5 is alkyl of 1 to 4 carbon atoms,

or an acid addition salt form thereof, comprising reacting a compound of formula II,



II

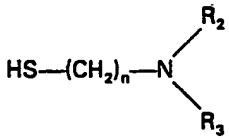
in which

R_1 is as defined above,

and

R_6 is alkyl of 1 to 4 carbon atoms or phenyl, unsubstituted or substituted by alkyl of 1 to 4 carbon atoms,

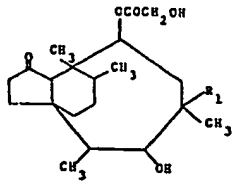
with a compound of formula III,



III

in which n, R_2 and R_3 are as defined above, characterised in that the reaction is effected in the presence of a phase transfer catalyst, and, where required, converting a resulting free base form of the compounds of formula I into an acid addition salt form, or *vice versa*.

2. A process according to Claim 1, in which the compound of formula II is produced by reacting a compound of formula IV,



IV

in which

R_1 is as defined in Claim 1, with a compound of formula V,

$$R_6SO_2A \qquad V$$

in which

A is the acid radical of a reactive ester.

3. A process according to Claim 1, in which the phase transfer catalyst is benzyltributyl-ammonium bromide or tetrabutylammonium bromide.

4. A process according to Claim 1, in which the reaction is effected by mixing a solution of the compound of formula II, in an inert, water-immiscible organic solvent with an aqueous solution of the compound of formula III or mixture of the compound of formula III with water.

5. A process according to Claim 4, in which the inert water-immiscible organic solvent is toluene.

6. A process for the production of a compound of formula I, as defined in Claim I, substantially as hereinbefore described with reference to any one of the Examples.

7. A compound of formula I, as defined in Claim 1, whenever produced by a process as claimed in any one of the preceding claims.

8. A process for the production of 14-desoxy-14-[(2-diethylaminoethyl)mercapto-acetoxy]-mutilin comprising reacting 14-desoxy-14-tosyloxy-acetoxymutilin with diethylaminoethanethiol hydrochloride under alkaline conditions and in the presence of a phase transfer catalyst.

9. 14-Desoxy-14-[(2-diethylaminoethyl)-mercaptoacetoxy]mutilin whenever produced by the process of Claim 8.

10. The compound of Claim 9, in hydrogen fumarate salt form.

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